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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,836	MENGE ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-12-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

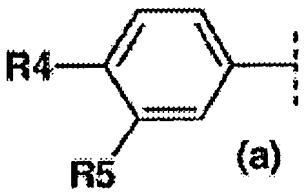
Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.

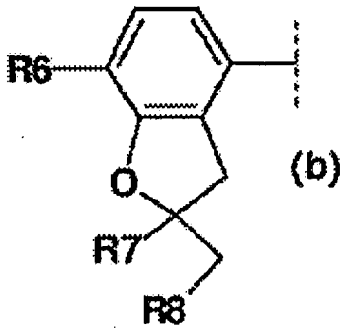
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-13, 15, 17 and 18, drawn to compounds of Formula I, wherein R3 is



, classified in class 540, subclass 524, class 544, subclasses 60, 114 and 238, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 217.05, 227.8, 236.5, 252.02 and 252.03.

II. Claims 1-12, 15, 17 and 18, drawn to compounds of Formula I, wherein R3 is



, classified in class 540, subclass 524, class 544, subclasses 60, 114 and 238, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 217.05, 227.8, 236.5, 252.02 and 252.03.

Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the benzofuranyl ring of Formula I, Group II, and the other phenyl ring of Formula I, Group I. The technical relationship among the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject substituted compounds of Formula I of Group I could not be used to reject substituted compounds of Formula I of Group II.

The Group I invention has special technical features not common to Group II and would be expected to be useful other than as disclosed, e.g., as anti-inflammatories (WO 2004018451).

During a telephone conversation with Mr. Sheldon McGee on Oct. 6, 2007 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-13, 15, 17 and 18. Applicant must affirm this election in replying to this Office action. Claims 1-12, 15, 17 and 18, to the extent they are directed to non-elected subject matter, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

To preserve a right to petition, the reply to this Office Action must distinctly and specifically point out supposed errors in the restriction requirement, or the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibition of PDE4BE activity, does not reasonably provide enablement for in vivo treatment of an illness treatable by PDE4 inhibition (claim 17) or of an airway disorder (including e.g., adult respiratory distress syndrome, chronic obstructive pulmonary disease, asthma, etc.) (claim 18). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not reasonably enable treatment of all pathological illnesses susceptible to PDE4 inhibition amelioration with Formula (I) compounds. The present specification offers no evidence that the claimed compounds control specific illnesses susceptible to PDE-4 inhibition amelioration, although the claims encompass such illnesses. The specification otherwise does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The following reasons apply to this enablement rejection.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D)

The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

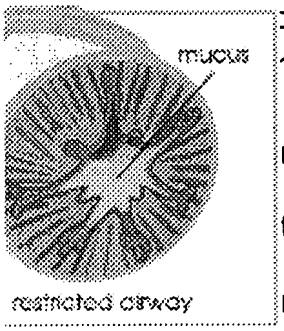
(1) Breadth of claims.

(a) Scope of the compounds.

The scope of the compounds is the trillions of compounds comprehended under formula I.

(b) Scope of the diseases covered.

Under diseases caused by PDE4 isozyme is Chronic Obstructive Pulmonary Disease (COPD) a collection of slowly progressive diseases of the airways, characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with



mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Acute respiratory distress syndrome (ARDS) is a life-threatening condition that causes lung swelling and fluid build up in the air sacs. ARDS is also known as Non-cardiogenic pulmonary edema; Increased-permeability pulmonary edema; Stiff lung; Shock lung; Acute respiratory distress syndrome; Acute lung injury. ARDS can be caused by any major lung inflammation or injury including pneumonia, septic shock, trauma, aspiration of vomit, or chemical inhalation. ARDS develops as inflammation and injury to the lung and causes a buildup of fluid in the air sacs, inhibiting passage of oxygen from the air into the bloodstream. The fluid buildup makes the lungs heavy and stiff, and the lungs' ability to expand is severely decreased. Blood concentration of oxygen can remain dangerously low in spite of supplemental oxygen. ARDS often occurs along with failure of other organ systems, e.g., liver or kidneys. Cigarette smoking and heavy alcohol use may be risk factors.

Asthma is a disease of the lungs that affects bronchial tubes or airways; a reversible obstructive airway disease. Unlike other conditions that obstruct airways, such as cystic fibrosis, chronic bronchitis and emphysema, asthma does not affect sufferers all of the time. During an asthma attack, membranes inside bronchial

tubes release mucus and become inflamed, causing muscles to contract and create wheezing spasms. Attacks can be severe or relatively mild, but the condition is dangerous and can easily spiral out of control. Specific causes of asthma are far from straightforward. Asthma is divided into a number of different types:

- **Allergic Asthma:** Triggered by allergens, e.g., pet dander, pollen, dust mites, pollutants, wood dust, smoke, irritants, chemicals, viral infections, bacteria, stress, emotion, exercise.
- **Childhood Allergic Asthma:** Maternal smoking can contribute to asthma or other infant lung function impairment, even before a child is born. Continued exposure to cigarette smoking can irritate the respiratory tract, making infants and children particularly vulnerable to allergic asthma.
- **Intrinsic Asthma:** Allergies do not play a part; its typical onset occurs after age 40. Possible causes include respiratory irritants, e.g., perfumes, cleaning agents, fumes, smoke, cold air, upper respiratory infections, gastroesophageal reflux. Intrinsic asthma tends to be less responsive to treatment than allergic asthma.
- **Exercise-Induced Asthma:** Can affect anyone at any age and may be attributed to loss of heat and moisture in the lungs with strenuous exercise. Frequent coughing during exercise may be the only symptom, but exercise-induced asthma symptoms can be more severe in cold, dry conditions. Prophylactic medications can prevent onset of asthmatic symptoms for sensitive individuals.

- **Nocturnal Asthma:** Affects people during sleep, regardless of time of sleep. Symptoms can be triggered by allergens in bedding or the bedroom, decrease in room temperature, and gastroesophageal reflux.
- **Occupational Asthma:** Occurs as a result of breathing chemical fumes, wood dust, or other irritants over long periods of time.
- **Steroid-Resistant Asthma:** Overuse of asthma medications can lead to status asthmaticus, a severe asthma attack that fails to respond to medication and may require mechanical ventilation.

IBD is another illness considered to be associated with PDE4 activity, a generic term for an entire disorder family, the most important of which are Ulcerative colitis and Crohn's disease. Less common forms include lymphocytic colitis, collagenous colitis, radiation enterocolitis, solitary rectal ulcer syndrome (SRUS), Antibiotic associated IBD, diversion colitis, Ischaemic Colitis, Behçet's Syndrome, and Infective Colitis.

IBD arises from a range of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Ischaemic Colitis arises from partial death tissue (infarct) due to blood supply blockage, e.g., after major abdominal surgery or poor cardiac output in heart disease. Radiation enterocolitis arises from cancer chemotherapy. Infective Colitis can arise from bacteria (e.g., Shigella, Salmonella, Campylobacter, E. coli) or Viruses (e.g., Norwalk-like virus rotavirus, CMV and HSV). Diversion Colitis develops from faecal stream diversion following colostomy or ileostomy. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no effective pharmaceutical treatment. IBD is a

generic term for a family of disorders, of which ulcerative colitis and Crohn's disease are most important. Less common forms are colitis (including lymphocytic, collagenous, diversion, ischemic and infective colitis), radiation enterocolitis, solitary rectal ulcer syndrome (SRUS), antibiotic associated IBD, and Behçet's Syndrome. IBD has a range of known and unknown causes. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Partial tissue death (infarct) due to blood supply blockage, e.g., after major abdominal surgery or poor cardiac output in heart disease, can cause ischemic colitis. Cancer therapy can cause radiation enterocolitis. Infective colitis can arise from bacteria (e.g., shigella, salmonella, campylobacter, E. coli) or viruses (e.g., Norwalk-like virus rotavirus, CMV, HSV). Fecal stream diversion after ileostomy or colostomy can cause diversion colitis. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no current effective pharmaceutical treatment.

Memory disorders, another illness considered to be associated with PDE4 activity, comprise all impairment of understanding or skill disorders. These include acquired language disorders, such as aphasias (e.g., conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia. It includes many types disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory about one specific event), Fugue amnesia (Psychogenic amnesia or hysterical amnesia, including "repressed memories"), Childhood amnesia (inability to remember events from early childhood), Transient Global Amnesia (total memory loss), those arising from complex

partial seizures, and alcoholic blackouts. It also includes various agnosias, such as Prosopagnosia, Integrative agnosias, asogmatoagnosia, Associative agnosias, Time Agnosia, Apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia, dyslexia, dyscalculia, right-left disorientation, Optic ataxia and Ocular apraxia, Color Agnosia, Simultanagnosia, Anosognosia, Auditory Agnosia (including amusia and word meaning deafness), and Somatosensory Agnosia (including Microsomatagnosia, Macrosomatagnosia, tactile agnosias and astereoagnosia), constructional dyspraxia, and more general processing disorders such as Cerebral Visual Impairment (CVI).

The claimed scope includes treating various illnesses, which are inadequately enabled, based on in vitro inhibition of PDE-4BE. The Formula (I) compounds are disclosed to inhibit PDE-4BE and the specification recites that these compounds are therefore useful to treat all illnesses susceptible to amelioration by PDE-4 inhibition for which Applicants provide no competent evidence. Further, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for the intended host.

Claims 17 and 18 are directed to methods for treating illnesses susceptible to PDE-4 inhibition amelioration. The claimed scope includes the recited disorders of the claims, as well as other known and as-yet undiscovered disorders/conditions that may be associated with PDE-4 now or in the future, for which the disclosure is non-enabling.

(2) The nature of the invention and predictability in the art:

The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance:

That provided is very limited. The dosage range information is vague and meager. Moreover, this is generic, the same for the many disorders covered by the specification. There is no specific direction or guidance regarding a regimen or dosage effective specifically for various compounds described for various illnesses comprehended.

(4) State of the Prior Art:

These compounds are 4H-pyridazine-3-ones with a particular substitution pattern. So far as the examiner is aware, no such compounds have been demonstrated in clinical studies to have PDE-4 inhibition activity, nor to useful for the treatment of the various illnesses construed by the claims.

Claim 17 states that these compounds treat any illness treatable by a PDE4 inhibitor. Dyke, et al., Exp. Opin. Invest. Drugs 8:1301-1325 (1999), comments on PDE-4 inhibitor efficacy in Parkinson's disease and learning and memory impairment as merely prophetic. Regarding MS, Dyke suggests, with no clinical data available, that PDE4 inhibitors may be useful as anti-inflammatory agents, but not as disease modifying agents (pg. 1313). Dyke's expert opinion was that, although PDE-4 inhibitors

showed some promise in the respiratory area, "clinical data in most [other] therapeutic areas with compounds of this class is inconclusive" (pg. 1314). Dyke acknowledges various PDE isoenzymes, but teaches that PDE-4 inhibitors have only been implicated for anti-inflammatory conditions (pg. 1302).

Hanifin, et al., Journal of Investigative Dermatology, 107(1):51-56 (1996) reported testing three PDE-4 inhibitors on atopic dermatitis. Hanifin supports that not all PDE-4 inhibitors are effective against atopic dermatitis.

The concept that PDE-4 inhibitors could treat all illnesses, based on in vitro inhibition of PDE4BE generally, is contrary to what is known about PDE-4 inhibitors. Some PDE4 inhibitors cause vasculitis (blood vessel inflammation), which has hindered PDE-4 inhibitor clinical investigation. Development of SCH-351591 halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was a significant problem with CI-1018 and Ariflo® (cilomilast). The PDE-4 inhibitor IC542 triggered a generalized inflammatory response with extensive neutrophil infiltration in the gastrointestinal tract, nearby mesentery and thymus.

(5) Working Examples:

The Examples show the production of a meager number of compounds from among the trillions covered by formula I. No biological data of any kind is presented. As stated in *Morton Intrntl. Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce

> the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

(6) Skill of those in the art:

The history of the actual effectiveness of PDE-4 inhibitors is very short. PDE-4 inhibitors have been investigated for disorders ranging from AD to COPD to depression to schizophrenia to chronic lymphocytic leukemia (CLL). Such efforts have met with very little success. The skill level in the area of PDE-4 therapeutics must therefore be considered to be low. At the time of filing and up to now, FDA has not approved any PDE-4 inhibitor for any disorder treatment. Extensive effort to get cilomilast and Daxas® (roflumilast) to be effective against COPD has been without success, evidence of the skill level in this art. Whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast is not described.

The state of the art indicates the requirement for undue experimentation. MacKenzie, Alergology International (2004) 53:101-110, indicates that, although the new generation of PDE-4 inhibitors "display[s] greatly reduced side-effects, ... further study of the potential ancillary involvement of adrenaline and/or glucocorticoids in the enhancement of PDE-4, shown in blood mononuclear white cells of [atopic dermatitis] patients is warranted." The ability of a PDE-4 inhibitor to ameliorate all illnesses construed by the present claims remains open to further study and proof.

(7) The quantity of experimentation needed:

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex*

parte Powers, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. See also MPEP 2163, *et. seq*. The disclosure in this application is insufficient to enable the instantly claimed methods based solely on disclosure of PDE4BE inhibition by Formula (I) compounds. Such experimentation is potentially open-ended.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-13, 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1: It is not understood what is meant by "completely or predominantly substituted by flourine." If the intended substituent is "predominantly" substituted by the recited substituent, what substitutes the other positions? What degree of substitution constitutes "predominant"? It is not understood what is intended by a "hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom." If a hydrocarbon ring has oxygen or sulphur ring members, it ceases to by a hydrocarbon ring. If the oxygen or sulphyr

ring members interrupt the hydrocarbon, are those included in or additional to the 5-7 membered ring?

In claims 17 and 18, the reference to "PDE4" is unclear. Four genes encode the PDE-4 family; there are actually four PDE-4 types, PDE-4A, PDE-4B, PDE-4C and PDE-4D, and these also occur in isoforms. Note that the specification uses only the single isoform PDE4BE for *in vitro* tests. The isoforms generally arise from presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2) and other pieces that may be present. UCR1 and UCR2 are shown to form a module necessary for PDE-4 activation upon cAMP-dependent kinase (PKA) phosphorylation. E.g., at least 5 different forms of PDE-4B: PDE-4B1, PDE-4B2 (the short form), PDE-4B3, PDE-4B4 exist and very recently discovered, PDE-4B5. Distinct PDE-4A isoforms include PDE-4A1, PDE-4A5, PDE-4A4B, PDE-4A7, PDE-4A8, PDE-4A10 and PDE-4A11. PDE-4D has 9 forms, which are not necessarily interchangeable and have substantial distribution variation even within sub-families. Thus, PDE-4A1 is abundant in the brain, PDE-4A4B and PDE-4A10 in inflammatory cells, PDE-4A7 in the brain and spleen, and PDE-4A11 is widely distributed. The PDE-4D family is generally not seen in inflammatory cells. PDE-4D1 is seen in spleen and heart, PDE-4D2 in spleen, PDE-4D3 in brains, lung and kidney, PDE-4D4 and PDE-4D6 in brain, PDE-4D5 in lung and kidney, PDE-4D7 in brain and testes, PDE-4D8 in lung, heart and liver, and PDE-4D9 in spleen, heart and lung. Different types are differently regulated. ERK MAP kinases phosphorylate and regulate activity of PDE-4B, PDE-4C and PDE-4D but not PDE-4A isoforms. Reduced PDE-4D activity apparently causes defective RyR2-

channel function associated with heart failure and arrhythmias. In dendritic cells (cells responsible for naive T_h cell priming), PDE-4A is predominantly active, whereas monocytes mainly express PDE-4B. PDE-4D5 isoform preferentially interacts with signaling scaffold proteins, β-arrestin and RACK1. PDE-4D3 likewise forms a signaling complex with AKAPs, e.g., AKAP450.

Rejections Under 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-13, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being obvious over Hatzelmann, et al., WO 2004018451, entitled to the filing date of 20030806.

Hatzelmann has a common assignee and two common inventors with the instant application. Based upon the earlier effective filing date of Hatzelmann, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in Hatzelmann was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in Hatzelmann, prior to the effective filing date of Hatzelmann under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that this application and Hatzelmann are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that Hatzelmann is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Hatzelmann describes piperidinylpyridazinones as inhibitors of phosphor-diesterase PDE4 or PDE3/4 inhibitors. See the Hatzelmann compounds of Examples 4, 5, and 8-31. The claimed compounds are lower alkyl homologs of the Hatzelmann

compounds, when the present compounds are further lower alkyl substituted on the 4-ring position of the 2H-pyridazine-3-one ring. Note that Hatzelmann (page 2, description of Formula 1 compounds) teaches that the 2H-pyridazine-3-one ring may be substituted in the 3- and 4-ring position by hydrogen or lower alkyl.

Presently claimed compounds that are lower alkyl homologs of Hatzelmann would have been obvious to one of ordinary skill in the art at the time of the present invention for the expected utility of the Hatzelmann compounds. One of ordinary skill in the art would have been motivated to prepare the claimed compounds as lower alkyl homologs of the Hatzelmann compounds, because such structurally related compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results.

> An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

In re Payne, 203 USPQ 245, 254 (CCPA 1979). See also *In re Papesch*, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1991) (discussed in MPEP § 2144) for an extensive case law review pertaining to obviousness based on close structural chemical compound similarity. See also MPEP § 2144.08, I[II.A.4(c). Compounds that are homologs (compounds differing by the successive addition of the same chemical group, e.g., by CH3-groups), as here, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In*

re Wilder, 195 USPQ 426 (CCPA 1977). Hatzelmann establishes a *prima facie* case of obviousness for the presently claimed compounds. Absent the presentation of verifiable data establishing the unobviousness of the claimed compounds over Hatzelmann, or other procedures as explained above, this rejection is deemed sound.

Objected Claims

Claims 1-12, 15, 17 and 18 are objected to as directed to both elected and non-elected subject matter. These claims should be amended to recite only elected subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.
10/21/2007

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